REMARKS

In the Office Action dated June 2, 2003, Claims 1-12 are pending. The Examiner has made the restriction requirement final. Therefore, Claims 1-10 are currently under consideration. The Examiner has objected to the Applicants' claim for priority of the related applications, i.e., the provisional application 60/074,193 and the parent application U.S. Application Serial No. 09/247, 396 ("the '396 application"). Claims 1, 3-7 and 9-10 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tjellstrom, et al. (*Acta Paediatr* 1997: 86:221-223) ("Tjellstrom, et al.") as evidenced by Eibl and Wolf (in "*Threrapeutic Immunology*", eds Augten, et al., 1996 Blackwell Sciences, Inc., Cambridge, Massachusetts, Chapter 22, "Immunoglobulin A", pages 297-310)("Eibl and Wolf") and the present application on page 10, at lines 29-31, stating that IgAbulin is an appropriate commercial immunoglobulin preparation for use in the instant methods. Claims 1-10 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over U.S. Patent No. 4,676,982 to Hassig ("Hassig") and U.S. Patent No. 4,477,432 to Hardie ("Hardie"). Claims 1-8 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Tjellstrom et al. as evidenced by Eibl and Wolf and the present application on page 10 at lines 29-31; in view of Hassig.

Applicants, through the undersigned, wish to thank Examiner Roark for the courtesy and assistance provided in connection with a telephonic interview conducted on August 26, 2003.

During the course of interview, Applicants explained to the Examiner, that the immunoglobulins in the present invention are pooled from many human individuals and

thus are non-antigen specific, polyclonal antibodies. Therefore, both recitations of "pooled human polyclonal immunoglobulin preparation" and "human immunoglobulin preparation" are fully supported by the priority applications. The Examiner indicated in the interview that the argument appeared to be persuasive. The Examiner required that Applicants show how the immunoglobulins are made.

As to the 103(a) rejection regarding Hassig and Hardie, Applicants argued during the interview that taken separately or combined together, Hassig and Hardie lack expectation of success and motivation for one skilled in the art to find the present invention obvious. However, agreement was not reached regarding this issue.

This response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

In an effort to expedite favorable prosecution, Claims 1, 4 and 9-10 have been amended and Claims 13-14 have been added. Support for the amendments can be found throughout the present application, on page 7, line 13 to page 8, line 28, for example. Support for the amendments can also be found throughout the priority applications, on page 9, line 9 to page 11, line 9 of the '396 application, for example. No new matter has been added.

Claims 11-12 have been withdrawn from the consideration. Applicants reserve the right to file a divisional application directed to the subject matter of Claims 11-12.

The Examiner has objected to the Applicants' claim for priority as allegedly lacking written support. In particular, the Examiner alleges that it is unclear if the "pooled human polyclonal immunoglobulin preparation" recited in the claims of the present application is supported by the "human immunoglobulin preparation" as disclosed in the priority applications.

In response, Applicants respectfully submit that both recitations of "pooled human polyclonal immunoglobulin preparation" and "human immunoglobulin preparation" are fully supported by the priority applications.

Applicants submit that in the Official Action dated May 22, 2000, with respect to the '396 application, Examiner Martha Lubet rejected Claims 1-2 and 4-7 of the '396 application under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,869,048 issued to Das ("Das"). In response to that Action, Applicants argued that Das does not teach the invention as disclosed in the '396 application. However, in an effort to expedite favorable prosecution, Applicants amended the claims in the '396 application to recite a "pooled human polyclonal immunoglobulin preparation." The amendment described in the '396 application delineated what is disclosed in the priority applications, i.e., a human immunoglobulin preparation pooled from many individuals which inherently comprised polyclonal and non-antigen specific immunoglobulins.

Applicants now further observe that Das and the '396 application disclose two different products and processes. While Das teaches a method for treating ulcerative colitis by administering a humanized monoclonal antibody, the '396 application discloses a method for treating inflammatory bowel disease (IBD) by administering a human

immunoglobulin preparation. In other words, Das employs monoclonal antibodies prepared from mice whereas the present invention employs pooled immunoglobulins prepared from human plasma, i.e., polyclonal, non-antigen specific, human antibodies. Applicants thus submit that, even without the amendment, the recitation of "human immunoglobulin preparation" in the original claims of the '396 application is distinguished from the prior art.

Assuming *arguendo*, as indicated by the Examiner, that a polyclonal antibody can be interpreted as antigen specific, Applicant directs the Examiner's attention to the fact that the specifications of both the present application and the priority applications disclose that the immunoglobulins of the present invention are pooled from human volunteers. *See, e.g.,* the present application on page 7, lines 13-23 and the '396 application on page 9, lines 9-23. Applicants submit that such pooled immunoglobulins from the human plasma as disclosed in the present invention are inherently polyclonal and non-antigen specific. Applicants also note that the Examiner, in the section 9 of the Official Action dated June 2, 2003, also admits that the intact immunoglobulin preparation obtained from (human) blood fractions "is a pooled human polyclonal immunoglobulin preparation." In fact, to Applicants knowledge, human monoclonal antibodies (mAb), i.e., mAb from a suitable human myeloma cell line, have not been successfully isolated to date.

Applicants further submit that the written description requirement does not require that the application disclose every detail that is well known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed Cir. 1986). A

critical element of the written description requirement calls for the Examiner to determine whether the applicant has demonstrated possession of the claimed invention. *MPEP* §2163. Applicants submit that the present invention discloses a pooled human immunoglobulin preparation which is inherently non-antigen specific and polyclonal, even though the application does not specifically use the term "polyclonal." Applicants further submit that, one skilled in the art would also recognize that Applicants were in possession of the claimed invention at the time the priority applications were filed.

Therefore, Applicants submit that claims reciting either "pooled human polyclonal immunoglobulin preparation" or "human immunoglobulin preparation" are allowable.

In addition, in a 102(b) rejection to the present invention, the Examiner cited Tjellstrom et al. The Examiner alleges that Tjellstrom et al. disclose IgAbulin and the present application discloses that IgAbulin is a commercial immunoglobulin preparation for use in the present invention. The Examiner then states that "IgAbulin must be a pooled human polyclonal immunoglobulin preparation." The Examiner thus concludes that the present invention has been allegedly anticipated by Tjellstrom et al. Applicants respectfully submit that the Examiner has interpreted the claims in the present invention inconsistently, i.e., in two different ways with respect to the written support and the prior art rejections.

Accordingly, in view of the amendments and the remarks above, the objection of the priority claimed upon the provisional and the parent application, is obviated and withdrawal thereof is respectfully requested.

Claims 1, 3-7 and 9-10 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tjellstrom, et al. as evidenced by Eibl and Wolf, and the present application on page 10, at lines 29-31.

Applicants note that the Examiner states in the Action that if adequate written support is established for the claimed priority in provisional application 60/074,193 and the '396 application, Tjellstrom, et al. would not be available as prior art.

In response, Applicants submit that the primary reference, Tjellstrom, et al., is not a prior art reference relative to the present application, in view of the argument above. Accordingly, the secondary reference (Eibl and Wolf) and the reference to the present application on page 10, at lines 29-31, do not sustain. Therefore, the rejection of Claims 1, 3-7 and 9-10 under 35 U.S.C. §102(b) is overcome. Withdrawal thereof is respectfully requested.

Claims 1-10 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Hassig and Hardie.

Applicants observe that Hardie is directed to the use of oral immunoglobulin in treating enteric infections (col. 7, line. 10). The invention of Hardie comes from the observation that "breast-fed newborn infants are better protected against gastrointestinal infection than formula-fed infants" (col. 1, lines 44-46). The study of infants in Hardie, exemplifying the invention, "demonstrates that the infants' stool contained significant quantities of undigested and intact IgG and that this coproantibody retained significant opsonic activity for Type III Group B *Streptococci*" (col. 6, line 67 to col. 7, line 3). Thus, Hardie concludes that, "[o]ral IG, therefore, may be used in prevention or treatment

of enteric infections, e.g. *E. coli, V. cholera, S. typhosa* or intoxications, e.g. botulism, since intact IgG with opsonic activity persisted in the gastrointestinal tract and thus is available to function in such prevention or treatment" (col. 7, lines 3-8). Hardie does not mention or refer to the treatment of inflammatory diseases. Furthermore, Hardie does not mention or refer to ulcerative colitis or Crohn's disease.

Applicants respectfully submit that it would have been clear to one skilled in the art at the time the present invention was filed that antibiotics could be used successfully to treat enteric infections which are caused by microorganisms or their products. It would also have been clear that antibiotics had been tried and were not effective in treating the majority of patients with IBD, such as those with ulcerative colitis or Crohn's disease, of which the etiology is not known. Thus, at the time of the present invention, one skilled in the art did not have the requisite motivation to extrapolate the invention of Hardie to the treatment of IBD with any expectation of success.

Applicants also observe that Hassig is directed to the use of intravenously injectable, polyvalent, intact immunoglobulin in the treatment of chronic inflammatory diseases of the bowel, e.g. ulcerative colitis and Crohn's disease (Abstract; col. 1, lines 6-8; and col. 4, lines 1-4 and 15-16). Applicants further observe that, in distinction to enteric diseases, caused by microorganisms or their products (such as are recited by Hardie, *supra*), Hassig notes that "[c]ertain inflammatory conditions of the bowel are of unknown etiology and are difficult to treat" (emphasis added, col. 1, lines 9-10). Hassig

goes on to specify ulcerative colitis (col. 1, line 11) and Crohn's disease (col. 1, line 13) as examples of these inflammatory conditions of "unknown etiology."

Applicants further submit that Hassig was filed when the Hardie patent had been issued. Hassig provides no suggestion or motivation that methods for the treatment of enteric infections (e.g., the methods of Hardie), the etiology of which was then known to be microbial, would have any application or utility in the treatment of the IBD which Hassig was seeking to treat. In fact, one of ordinary skill in the art at the time of the present invention would not have connected the "opsonic activity" of the IgG in the gut, remarked upon by Hardie, *supra*, with the anti-inflammatory activity of these same materials when delivered intravenously. The high molecular weight of immunoglobulin or IgG would be well known to one skilled in the art to prevent the transport of these molecules from the gut to the bloodstream. In addition, the Tjellstrom et al. reference cited by the Examiner, *supra*, teaches that intravenous immunoglobulin treatment has yielded varying results. *See* paragraph 1. The specification on page 4, line 30 to page 5, line 3, also indicates that treatment of IBD by intravenous administration of immunoglobulins has been investigated with inconsistent results, by citing Levine D.S., et al., 1992 *Am. J. Gastroenterol.* 87:91-100; Wolf A., et al., 1988 *Mschr. Kinderheilk* 136:101-103; Knoflach P., et al., 1990 *Ann. Intern. Med.* 112*:385-386;* Schmidt, C., 1990 *Klinikarzt* 19:552-558; and Canva-Delcambre, V. 1996 *Aliment. Pharmacol. Ther.* 10:721-727). Accordingly, Applicants respectfully submit that at the time of the present invention the method of treating IBD by intravenous administration of immunoglobulins would not have met with any expectation of success. To substitute the method of Hassig

with oral administration taught by Hardie for treating IBD, one skilled in the art had to be motivated merely based on speculation.

Thus, it is surprising, and not obvious from the art, that the inventor of the present application discovered that immunoglobulins would be effective in treating an inflammatory condition such as ulcerative colitis or Crohn's disease.

Accordingly, the examiner's combination of the Hassig and Hardie can, in fact, only be made with the benefit of hindsight, derived from the disclosure of the present application. In addition, assuming *arguendo* one is motivated from the disclosure of Hassig to use an immunoglobulin preparation for the treatment of inflammatory bowel disease, there is no expectation of success.

Furthermore, Applicants submit that the rejection of claimed subject matter under 35 U.S.C. §103 requires that the suggestion to carry out the claimed invention must be found in the prior art, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 492, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991). Here, the suggestion to use the claimed methods to treat IBD by orally administering to a patient an effective amount of a human immunoglobulin preparation appears nowhere in the cited combination of Hassig and Hardie. Therefore, Applicants respectfully submit that the claimed methods are not obvious in light of Hassig and Hardie.

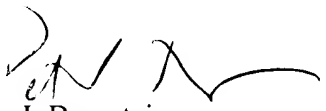
In view of the above remarks and the amendments, it is respectfully submitted that the present invention is non-obvious in view of Hassig and Hardie. Accordingly, the rejection of Claims 1-10 under 35 U.S.C. 103(a) is overcome and withdrawal thereof is respectfully requested.

Claims 1-8 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Tjellstrom et al. as evidenced by Eibl and Wolf and the statement on page 10 at lines 29-31 of the present application; in view of Hassig.

Applicants submit that the primary reference, Tjellstrom, et al., is not a prior art reference relative to the present application, in view of the argument above. The secondary references (Eibl and Wolf, Hassig) and the statement on page 10 at lines 29-31 of the present application do not sustain. Therefore, the rejection of Claims 1, 3-7 and 9-10 under 35 U.S.C. §103(a) is overcome. Withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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